REMARKS/ARGUMENTS

Claims 7-21 remain in this application. Claims 1-6 have been canceled. Claims 7, 9, 13, 14, 17, 18, 20 and 21 have been amended.

I. The Objection to the Specification

The Office Action objects to the specification asserting that the Accession No. for aggrecanase –1 and-2 quoted on page 8, lines 12-13, is invalid.

Applicants submit herein the results of a search on the NCBI database, which demonstrate that Accession Nos. NM 005099 and NM 007038 are valid Accession numbers for aggrecanase –1 and aggrecanase –2. Reconsideration and withdrawal of the objection to the specification are respectfully requested.

II. The Objection to the Drawings

The Office Action maintains the objection to Fig. 2, maintaining that the units of relative activities are not defined.

In response, Applicants respectfully submit that the specification discloses that the units for the y-axis are relative activities for the 56 aggrecanase –1 and –2 peptides set forth on the x-axis. See, e.g., page 16 and Fig. 2. The activities shown are relative activities to one another. One skilled in the art can readily ascertain, upon review of Fig. 2, which peptides have higher and which peptides have lower activity. Thus, the disclosure at p. 16 and in Fig. 2 is clear. Reconsideration and withdrawal of the objection to Fig. 2 are respectfully requested.

III. The Rejection Under 35 U.S.C. § 112, Second Paragraph

The Office Action rejects claims 7-13 under 35 U.S.C. § 112, second paragraph, asserting that (1) use of the term "truncated aggrecanase" and "aggrecanase" is confusing; (2) claim 9 is incomplete; (3) claim 13 is confusing for reciting contacting an already truncated aggrecanase; (4) claims 14-16 omit an essential step; and (5) "a position of a complete native sequence" as recited in claim 20 is not defined in the specification.

In response to the enumerated items above, Applicants (1) amend the claims to distinguish wild type aggrecanase from truncated aggrecanase; (2) complete claim 9 in accordance with claim 9 as originally filed; (3) amend claim 13 to clarify that the truncated aggrecanase is in a cell expressing the truncated aggrecanase; (4) amend claim 14 to clarify that measuring involves determining a presence or absence of cleavage of the peptide; and (5) amend claim 20 to clarify that the truncated aggrecanase lacks a "portion" of a complete native sequence (support can be found in the specification at, e.g., page 5, lines 15-26). Reconsideration and withdrawal of the rejection are respectfully requested.

IV. The Rejection Under 35 U.S.C. § 112, First Paragraph

The Office Action rejects Claims 7-21 under 35 U.S.C. § 112, first paragraph, asserting that (1) "neither the claims nor the specification teach that that the inhibitor of the truncated form of aggrecanase inhibits also the full length enzyme"; (2) although Applicants disclose several representatives of the claimed genus of polypeptides, Applicants "fail to disclose any particular structure to function ... relationship for a polypeptide that is less than 40 amino acids in length..."; (3) "[t]he data presented in Fig. 2 clearly prove that predictability of the function of the representatives of the claimed genus is not apparent; (4) the claims are not limited to the truncated forms of aggrecanase consisting of metalloprotease domains; (5) the limitation "homologues" in claim 21 consists of new matter; (6) "while being enabling for methods to detect compounds that inhibit aggrecanase using peptides of SEQ ID NO: 3, 4, 5, 6 and 7, that are cleavable by polypeptides of SEQ ID NO: 8 and/or 9 and human aggrecanase –1 and –2, does not reasonably provide enablement for methods to detect compounds that inhibit any aggrecanase using any peptide less than 40 amino acids in length comprising a cleavage site for any aggrecanase, its truncate forms and their homologs...".

Applicants respectfully submit that the subject matter of claims 7-21 is clearly disclosed in the present specification. Applicants will address the (6) enumerated points above: In response to (1), the present specification discloses that:

> The Aggrecanases used in this invention can be full length, partial, truncated, chimeric or modified enzymes that still retain their ability to cleave the peptides as described in this invention. It has been demonstrated that Aggrecanase cleavage sites in aggrecan contain glutamic acid on the N-terminal side of the cleavage site (P-1 position) and a non-polar or uncharged residue on the C-terminal side of the cleavage site (P1' position)...

See page 8, lines 14-29. Thus, consistent with the understanding in the art, the truncated activities retain the expected activity.

In response to (2), the present specification discloses (a) that the peptides "included a collection of substrates for other proteases, as well as a number of sequences corresponding to membrane proximal cleavage sites of various proteins postulated to be released by metalloproteases" (see page 15, lines 16-20); (b) that two of the peptide sequences employed had particularly good activity (see page 16, lines 3-13); and (c) that additional peptides can serve as peptide substrates in accordance with the invention (see page 8-31). Thus, as disclosed in the specification "those of ordinary skill in the art could similarly identify other [peptides] and test them in assays of this invention..."

In response to (3), Applicants respectfully submit that the data presented in Fig. 2 would aid one of ordinary skill in the art to employ those peptide sequences having higher activity to identify other peptide sequences that are capable of being cleaved by the truncated aggrecanases of the invention (see, e.g., page 5, lines 16-18; and page 6, lines 1-10).

Applicants should not be limited to the sequences specifically disclosed herein, but rather should be entitled to those peptides that can be identified in accordance with the invention.

In response to (4), the claims have been amended to clarify that the truncated forms are employed in the method of the invention.

In response to (5), Applicants have amended claim 21 to obviate this aspect of the rejection.

In response to (6), Applicants respectfully submit that the present specification provides sufficient guidance to enable one of ordinary skill in the art to detect compounds that inhibit aggrecanase. The specification provides peptide sequences that have proven useful as substrates in an assay to detect aggrecanase activity. The specification discloses that one of skill in the art can employ these peptide sequences to identify additional peptide sequences having the desired activity. The specification further discloses two truncated forms of aggrecanase that maintain the desired enzymatic activity and that these two forms can be employed in combination with the identified (and identifiable) peptides in an assay to identify inhibitors of aggrecanse. Reconsideration and withdrawal of the rejection of claims 7-21 under 35 U.S.C. § 112, first paragraph, are respectfully requested.

V. The Rejection Under 35 U.S.C. § 103

The Office Action rejects claims 7-9, 11-13 and 20-21 under 35 U.S.C § 103 as being obvious over Tortorella et al., J. Biol. Chem., 275(33):25791-25797 (2000). In particular, the Office Action asserts:

> Tortorella et al. disclose (page 4, line 3, of the Internet print out of the article) polypeptide NITEGE-ARGS consisting of less than 40 amino acids and comprising cleavage site E-A i.e. cleavage site between a glutamic acid on an N-terminal side of the cleavage site and a non-polar or uncharged amino acid residue (in this case alanine) on a C-terminal side of the cleavage site. Tortorella et al. teach that both the full length and truncated aggrecanase-1 cleave that substrate. Tortorella et al. does not teach the use of this peptide for identification of inhibitors of aggrecanase/its truncated form.
>
> It would have been obvious ... to have the peptide disclosed by Tortorella et al. as a substrate for truncated aggrecanase and use it for screening for inhibitors of the aggrecanase.

Applicants respectfully traverse the rejection.

Tortorella et al. disclose a study to determine whether aggrecanase-1 recognized aggrecan through binding of TSP-1 motif to the aggrecan glycosaminoglycans, chondroitin sulfate and keratin sulfate, and whether binding of the enzyme to these glycosaminoglycans is important for cleavage of the core protein. See page 3. Although Tortorella et al. disclose that both full length and truncated aggrecanase-1 cleaved a peptide substrate containing the

aggrecanase-sensitive cleavage site NITEGE-ARGS, the reference does not disclose that the size of the peptide is 40 amino acids or less. In a later publication, Tortorella et al. disclose:

> Cleavage of cartilage *aggrecan* within the IGD between amino acids Glu^{373} and Ala^{374} *results in the formation of* a small N-terminal fragment with a new C-terminus $NITEGE^{373}$ and a large C-terminal fragment with the new N-terminus $^{374}ARGSV$.

(Emphasis added). See Tortorella et al., The role of ADAM-TS4 (aggrecanase-1) and ADAM-TS5 (aggrecanase-2) in a model of cartilage degradation, Osteoarthritis and Cartilage, 9:539-552 (2001) at page 540. Thus, although Tortorella et al. referred to a specific cleavage site, Tortorella et al. did not disclose or suggest the use of a peptide consisting of less than 40 amino acids in an enzymatic assay. Reconsideration and withdrawal of the rejection of claims 7-9, 11-13 and 20-21 under 35 U.S.C § 103 as being obvious over Tortorella et al. are respectfully requested.

Early consideration and prompt allowance of the pending claims are respectfully requested.

Respectfully submitted,

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